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THE EFFECT OF DANTROLENE SODIUM ON INTRAFUSAL MUSCLE FIBRES IN THE RAT SOLEUS MUSCLE

BY G. C. LESLIE AND N. J. PART
From the Department of Physiology, The University, Dundee DD1 4HN

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SUMMARY

1. The action of the skeletal muscle relaxant drug, dantrolene sodium, given intravenously, on the intrafusal fibres of the soleus muscle of the urethane-anaesthetized rat has been investigated. The experiments were made on functionally single spindle afferents and gamma fusimotor fibres isolated in dorsal and ventral roots respectively.

2. Dantrolene sodium was without effect on the discharge of primary and secondary afferents from the passive muscle spindle, nor were the dynamic indices of these endings affected.

3. Intrafusal muscle contraction was measured indirectly by means of the spindle afferent discharge.

4. The intrafusal muscle twitch contraction, as measured by means of the amplitude of the frequencygram, was depressed more slowly to a lesser extent than was the twitch of the extrafusal contraction.

5. Intrafusal contraction resulting from tetanic stimulation of the gamma fibre was depressed by dantrolene sodium to an extent dependent upon the stimulation frequency. At frequencies of 10, 25 and perhaps 50 Hz the depression was complete, that is, no afferent response was evoked; at 200 Hz stimulation, the depression was minimal (or non-existent).

6. For a muscle spindle primary ending under dynamic gamma activation dantrolene sodium caused a reduction of dynamic index whereas for the ending under static activation it caused an increase.

7. The significance of these findings in terms of the clinical use of the drug is considered.

INTRODUCTION

Dantrolene sodium (Dantrium, Eaton Laboratories, U.K.) is a muscle relaxant which acts by reducing the release of calcium from the sarcoplasmic reticulum (Ellis & Carpenter, 1972; Yamamoto, Suzuki & Hotta, 1977). The action of this drug on extrafusal skeletal muscle has been extensively studied (Nott & Bowman, 1974; Bowman, Houston, Khan & Rodger, 1979; Leslie & Part, 1981) whereas there is only one often quoted abstract report in the literature on its action on intrafusal muscle (Zorychta, Esplin, Capek & Lastowecka, 1971). These workers state that dantrolene sodium 'prevents the acceleration of spindle discharge' caused by gamma nerve fibre

stimulation. Any depression of intrafusal muscle fibre contraction will cause a reduction of the excitation of the alpha motoneurones through the muscle spindle afferent spinal reflexes. It is possible, therefore, that some of the extrafusal muscle-relaxant properties of dantrolene sodium in the intact animal or human patient may indirectly be due to any action on intrafusal muscle. A more detailed knowledge of the action of dantrolene sodium on intrafusal muscle is essential as a first step in the consideration of this problem.

Since intrafusal muscle contraction generates such extremely small tensions (Diete-Spiff, 1967) and furthermore is technically difficult to record we have not attempted the direct measurement of these tensions. Instead we have used the spindle sensory endings as transducers for the intrafusal muscle contraction.

If the sensory endings of the spindle are to be used as transducers for the contraction of the intrafusal muscle it is essential first to establish whether the drug has any direct action on the sensory ending. In this paper we do in fact establish that dantrolene sodium is without effect on the action of the spindle sensory ending, in agreement with the findings of Zorychta *et al.* (1971).

Our findings as to the action of dantrolene sodium on the intrafusal contraction are in disagreement with those of Zorychta *et al.* (1971) in that we do not find a total prevention of the acceleration of muscle spindle discharge produced by the stimulation of gamma fibres. Nevertheless we do find that dantrolene sodium reduces the increase in spindle afferent discharge frequency produced by gamma stimulation and hence, we would infer, the contraction of the intrafusal muscle.

A preliminary communication of some of these results was given to the Physiological Society (Leslie & Part, 1980).

METHODS

The experiments were carried out on a total of twenty-two Sprague Dawley female rats, 300–450 g body weight. Anaesthesia was induced with trichlorethylene vapour and maintained by intraperitoneal injection of urethane solution, dosage 1·5 mg urethane per g body weight. Supplementary injections were given as necessary.

The muscle used in these experiments was the soleus. Details of the preparation for the use of the rat soleus for spindle experiments are given by Andrew, Leslie & Part (1978). Briefly, single spindle afferent nerve axons were isolated in dorsal root filaments whilst single gamma fibres, active to the same spindle, were isolated in ventral root filaments. The response of the spindle afferent was recorded at constant length and during ramp and sinusoidal length changes with and without simultaneous stimulation of the gamma efferent fibre. The properties of the intrafusal muscle were also investigated using the frequencygram technique of Bessou, Laporte & Pagès (1968). The discharge of the passive spindle was displayed as an interspike interval histogram, generated with a multianalyser (DL4000, Datalabs Ltd.). The contraction of the soleus muscle was recorded by means of a tension transducer attached to the arm of the electromagnetic puller.

The dantrolene sodium was dissolved at 1 mg per ml. in a carrier of a sodium hydroxide solution at pH 10·3 made isotonic using 5% mannitol. The carrier solution, with and without dantrolene sodium, was injected into the femoral vein. The carrier alone is without effect on extra- and intrafusal muscle contraction (Leslie & Part, 1980). The final concentration of dantrolene sodium in the animal was 5 mg per kg body weight. This concentration of drug was shown in preliminary experiments to cause a maximal depression of extrafusal muscle twitch and is also approximately the maximum concentration at which the drug is used clinically.

RESULTS

The effect of dantrolene sodium on the passive spindle

The discharges of passive spindle endings, both primary and secondary, were displayed as interspike interval histograms. This technique is sensitive in revealing any alteration in the discharge of the ending; any change in the mean frequency of discharge will be revealed as a shift in the peak of the histogram and any change in

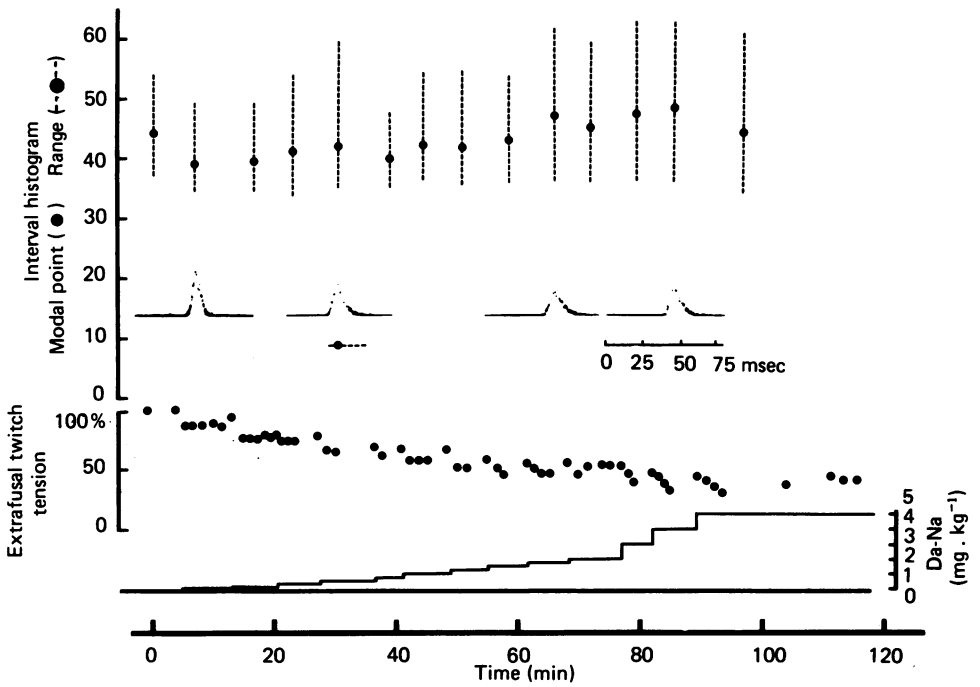

Fig. 1. Dantrolene sodium (Da-Na; 5 mg . kg^{-1}) is without significant effect on the modal point and range of interspike interval histograms (see insets), of a passive secondary endorgan (conduction velocity = 39·6 m . sec^{-1}). This was confirmed for primary and secondary endings in five other experiments. In contrast the amplitude of the whole soleus muscle extrafusal twitch was reduced from control values (≡ 100 %) to approximately 40 %.

the regularity of the discharge will be revealed as a change in the shape of the histogram. Fig. 1 shows that intravenous injection of dantrolene sodium is without effect upon both the mean rate and regularity of the resting discharge of the passive muscle spindle. This experiment shows that dantrolene sodium does not alter the static properties of the spindle. Measurements of the dynamic index were also taken before and after the injection of dantrolene sodium. The drug did not have any detectable effect on the dynamic index of either passive primary or secondary endings. This point is shown for two primary endings in the graphs of Fig. 4.

These results indicate that dantrolene sodium does not interfere with the transduction process of the spindle sensory endings. It is therefore in order to use the sensory endings to record, *indirectly*, the contraction of the intrafusal muscle.

The effect of dantrolene sodium on the fusimotor response

Four tests were applied, before and after the injection of dantrolene sodium, to determine the effect of the drug on the contraction of intrafusal muscle fibres:

(1) The frequencygram was used as a representation of the intrafusal muscle twitch. We have found, in the rat, that satisfactory frequencygrams could be obtained only from the combination of static gamma fibres with secondary spindle endings.

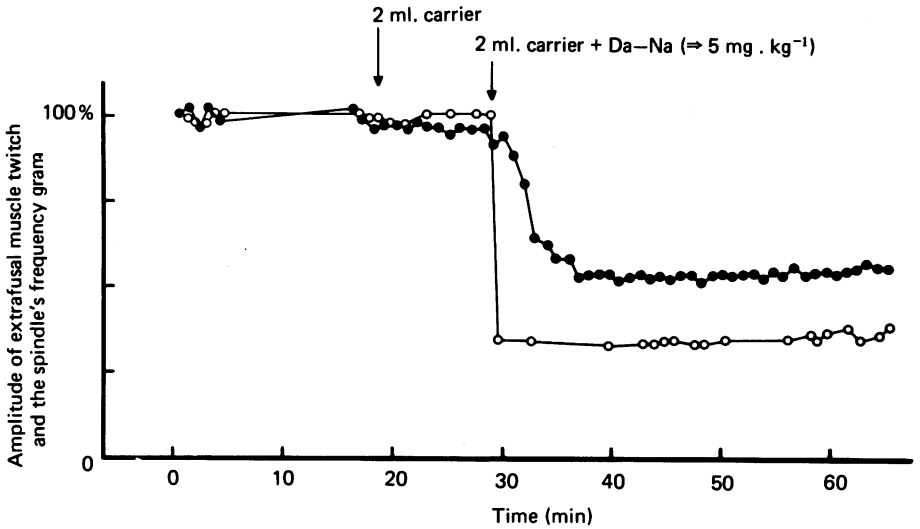

Fig. 2. Dantrolene sodium (Da-Na; 5 mg . kg^{-1}) produces rapidly, within a minute, a large (65%) decrease in the amplitude of extrafusal twitch (○). Intrafusal contractions monitored indirectly using the amplitude of the frequencygram (●) show a less marked reduction (= 45%) which is attained more slowly over some 10 min. The carrier solution alone (5% mannitol at pH = 10·3) is without significant action. The experimental records from which these graphs were constructed have been published in part as Fig. 1, Leslie & Part (1980). The conduction velocity of the secondary afferent fibre was 36·3 m . sec^{-1} and that of the γ-static, 27·9 m . sec^{-1}.

(2) With muscle length held constant the gamma fibre was stimulated at a number of frequencies between 10 Hz and 200 Hz for periods of 0·5 sec and the response of the spindle afferent, primary or secondary, was recorded as an instantaneous frequency display.

(3) The dynamic index was measured at a number of gamma fibre stimulation frequencies.

(4) The response of the spindle ending to sinusoidal stretch was recorded, with and without gamma fibre stimulation. The results from these four tests will now be given:

(1) *Frequencygram*

Fig. 2 shows the comparative reductions in the amplitudes of frequencygram and extrafusal muscle twitch produced by intravenous dantrolene sodium. The original records from which these results are taken have been published as Fig. 1 of Leslie & Part (1980). The rate of decrease and the final percentage reduction of the

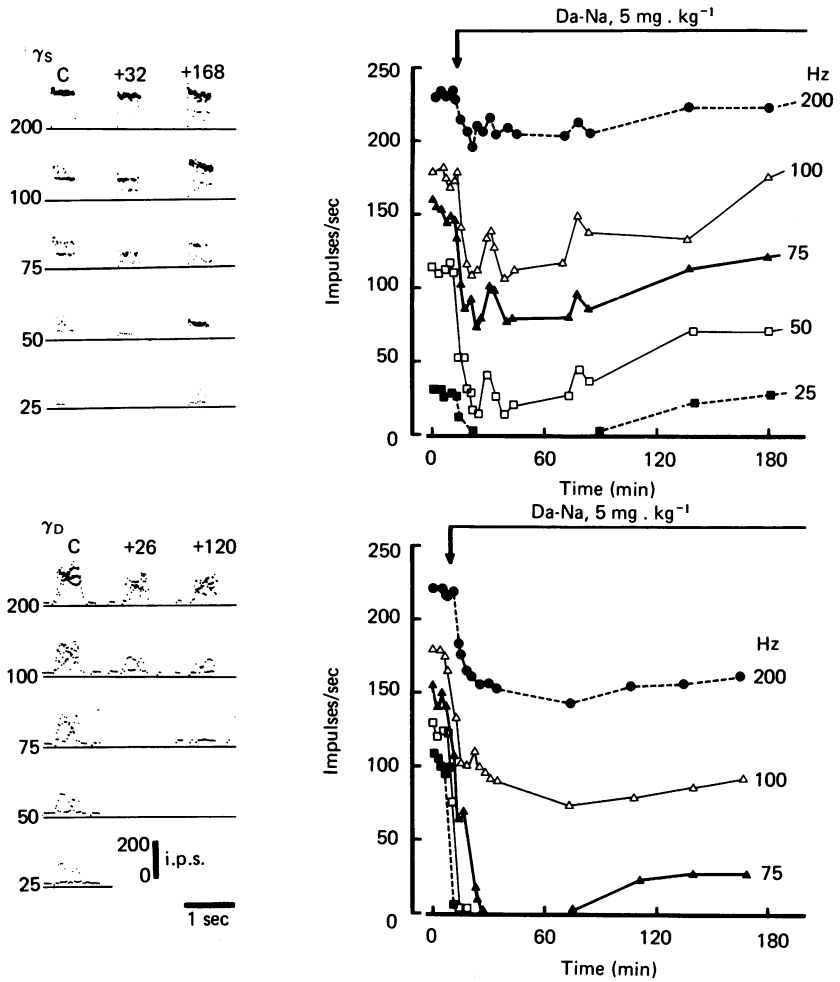

Fig. 3. Increases in frequencies of spindle afferent discharges evoked by fusimotor stimulation (10–200 Hz), with the muscle held at constant length, are reduced in magnitude or abolished when dantrolene sodium (Da-Na) is present. These reductions or abolitions occurred most noticeably at the lower frequencies of stimulation, and more so with the dynamic gamma fibres. Examples of instantaneous frequency analyses of spindle discharges with full graphic presentations from the same experiments are shown. The upper half of the figure contains results obtained with a primary ending, acted upon by a gamma static; results in the lower half are from a combination of a primary ending with a dynamic gamma. The figures to the left of the columns of traces showing instantaneous frequency analyses, and to the right of the lines on the graphs are the stimulation frequencies (Hz) to the gamma fibres; the continuous line below each row of traces represents zero frequency in the analysed recordings; the left-hand columns in each panel are controls before dantrolene sodium. Numbers above the two columns to the right represent time in min after drug injection.

frequencygram amplitude are less than those of the extrafusal muscle twitch amplitude. On average the frequencygram amplitude was maximally reduced by 37·2 ± 5·0 % (mean ± S.E. of mean, $n = 5$) whereas the soleus extrafusal muscle twitch amplitude was reduced by 64 ± 1·9 % (mean ± S.E. mean, $n = 10$).

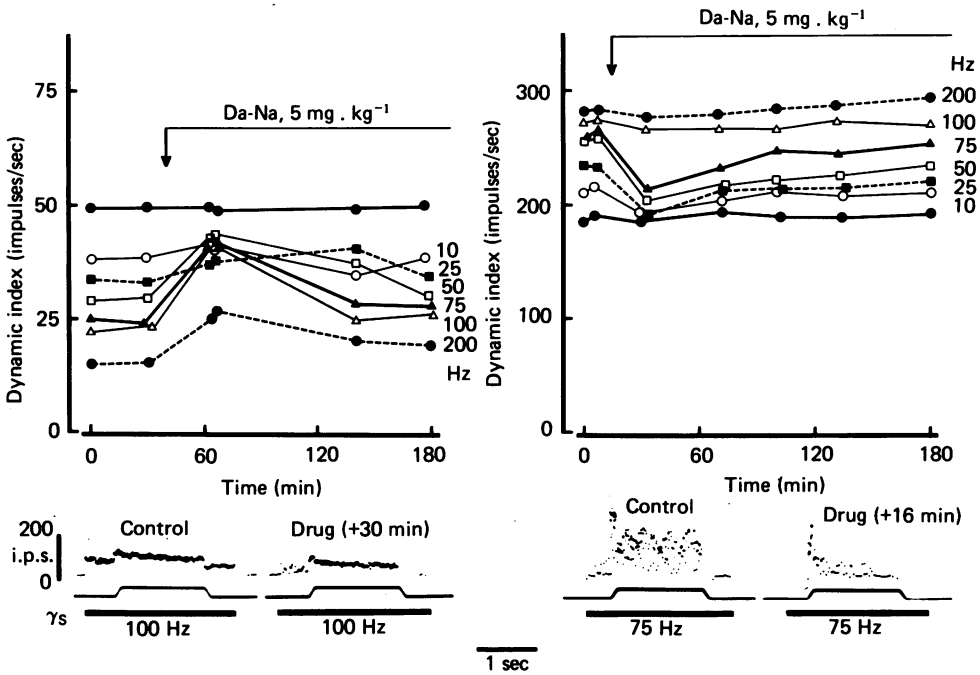

Fig. 4. Changes of dynamic index are shown for a static gamma fibre (on the left) and a dynamic gamma fibre (on the right), stimulated at frequencies between 10 and 200 Hz. With static fusimotion the dynamic indicies are most changed, with dantrolene sodium present, at frequencies of 50–100 Hz; in this illustration there exists even at 200 Hz a decrease in the effectiveness of reducing dynamic index; in the majority of our sample the change of dynamic index with dantrolene sodium and 200 Hz stimulation was minimal. For dynamic gamma fibre activity the maximum, frequency-dependent, changes are in the range 50–75 Hz; the action of the dynamic gamma at 100–200 Hz is little affected. Note the considerable recovery of intrafusal responses from the action of dantrolene sodium within 2 hr. (See text). The two sets of traces below the graphs are sample recordings of instantaneous frequency analyses of sensory discharges from two primary endings subjected to ramp extension of 1 mm applied to the soleus distal tendon at 10 mm/sec.

(2) *Instantaneous frequency displays at constant muscle length*

Fig. 3 illustrates experiments with both static and dynamic gamma fibres. Dantrolene sodium causes a depression of the response of the ending which is frequency-dependent. The effect of dantrolene sodium, however, cannot be followed for all the stimulation frequencies because at some low frequencies the ending fails to respond altogether and thus to act as a transducer. These graphs show that there is an appreciable recovery of the intrafusal response within an hour of the injection of dantrolene sodium, in contrast to results obtained from extrafusal muscle (Kotsias & Muchnik, 1978; Leslie & Part, 1981).

(*3*) *The effects of dantrolene sodium on the dynamic index*

The dynamic index is a well established measure of the dynamic sensitivity of the muscle spindle (Crowe & Matthews, 1964). As a static gamma fibre is stimulated at increasing frequencies, so is the dynamic index of the spindle sensory ending reduced. Conversely, for a dynamic gamma fibre the dynamic index is increased with increasing stimulation frequency (see Fig. 4). Fig. 4 also shows what happens to these changes in dynamic index when dantrolene sodium is injected intravenously. The action of dantrolene sodium on dynamic index depends upon the type of gamma nerve fibre, static or dynamic. In the case of the static gamma fibre the dantrolene sodium reduces the reduction of dynamic index produced by static gamma fibre stimulation; in other words, the dynamic index is greater at any given frequency of static gamma fibre stimulation in the presence of dantrolene sodium. This effect is frequency-dependent; the greatest reduction of the dynamic index reducing capacity of static gamma fibre stimulation is at intermediate stimulation frequencies (50–100 Hz). At the highest stimulation frequency (200 Hz) in this example the dantrolene sodium has some effect on dynamic index. In the majority of examples, changes of dynamic index by static fusimotor stimulation at 200 Hz were unaffected in the presence of the drug.

Considering now dynamic gamma fibres, dantrolene sodium acts to reduce the increase in dynamic index brought about by stimulation of the dynamic gamma fibre. The action of the drug is again dependent upon the stimulation frequency, the greatest effect being produced at intermediate stimulation frequencies, in this case at 50–75 Hz. At stimulation frequencies of 100 and 200 Hz, dantrolene sodium is without effect upon the dynamic index.

Fig. 4 shows results typical of five experiments with static gamma fibres and four dynamic gamma fibres, in all of which there was, within 2 hr, recovery from the effects of intravenous dantrolene sodium (cf. Fig. 3).

(*4*) *Sinusoidal stretching of spindle endings*

Fig. 5 shows instantaneous frequency analyses of spindle sensory discharges during 3 Hz sinusoidal stretching of the muscle, with and without fusimotor stimulation, before and after administration of the drug. Observations from a sample of seven static gammas and three dynamic gammas reinforced our general findings from the preceding sections: that the drug produces its maximum effect more slowly at the intrafusal fibres than at the extrafusal muscle fibres; that it weakens intrafusal contractions in a frequency dependent manner; that the action of dynamic gamma fusimotor fibres is less able to increase dynamic sensitivity compared to control levels and that the static component of the dynamic gamma activity is also effectively weakened; that static gamma fibres are less able to reduce the dynamic response; and that relatively the intrafusal muscle fibres are less affected and for a shorter time when compared with the muscle relaxant property of dantrolene sodium on extrafusal muscle.

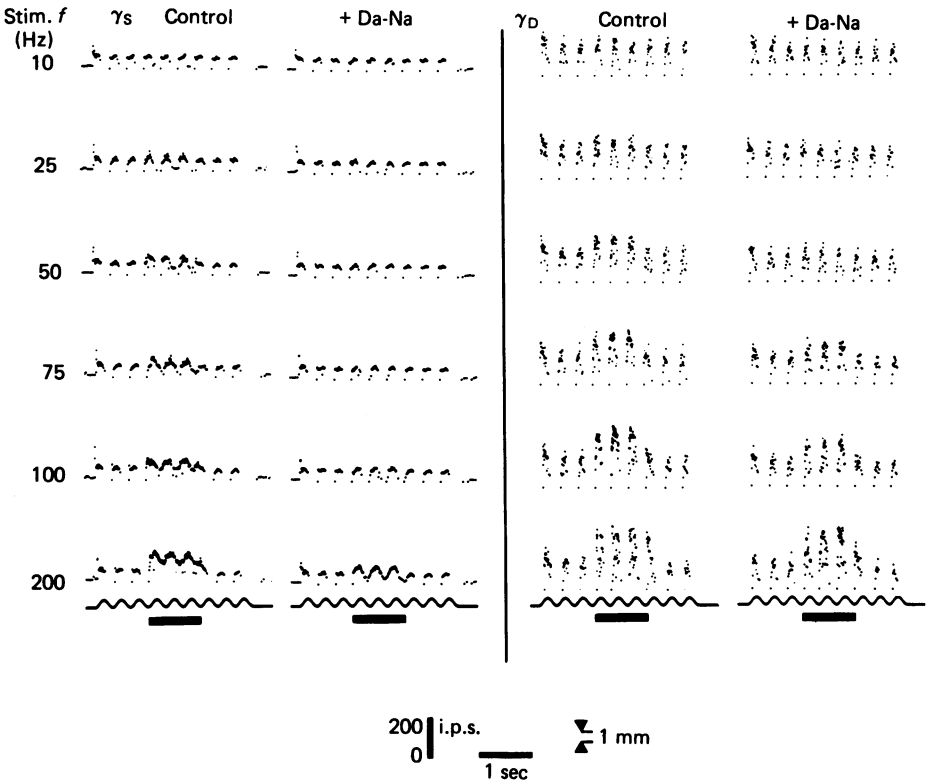

Fig. 5. Shows instantaneous frequency analyses of afferent fibre discharges from two primary endings subjected to 3 Hz sinusoidal stretching by 1 mm extension of the soleus muscle, and to various frequencies of fusimotor stimulation (10–200 Hz, during the bar marking) applied to a static gamma fibre (see two columns to left of mid line) and a dynamic gamma fibre (right of mid line). The sets of traces to the left in each panel are the controls, before intravenous dantrolene sodium. The action of the drug on intrafusal mechanics is clearly seen to be effective in modifying the discharge patterns evoked by fusimotion and to be related to the frequencies of fusimotor stimulation.

DISCUSSION

This investigation of the effect of dantrolene sodium on the contraction of intrafusal muscle involves the use of the spindle sensory endings as transducers of the intrafusal muscle contraction. This method is acceptable, in that dantrolene sodium is without action on the spindle sensory ending itself, but is limited by the inability of the ending to discharge at frequencies less than zero impulses per sec. Thus, when recording the effects of gamma nerve fibre stimulation on the discharge of a spindle ending without any resting discharge, as is often the case in the rat spindle (Andrew, Leslie & Thompson, 1973), that portion of the intrafusal contraction which is subthreshold for the production of afferent discharge goes unmonitored. Hence changes of afferent discharge frequency produced by dantrolene sodium will not give a totally undistorted recording of the underlying changes in intrafusal muscle contraction. Against this drawback must be put the fact that it is the spindle afferent

discharge into the spinal cord which the central nervous system sees rather than any other monitor of intrafusal muscle activity and so our method is certainly useful when considering the action of dantrolene sodium in the intact animal (see below).

These experiments have shown that dantrolene sodium (5 mg/kg) has a depressant action on the contraction of rat intrafusal muscle at the same concentrations at which it depresses extrafusal rat muscle contraction; similar concentrations of dantrolene sodium are without significant action on cardiac or smooth muscle (Ellis, Castellion, Honkomp, Wessels, Carpenter & Halliday, 1973). However, the drug produces more slowly a lesser depression of the contraction of intrafusal muscle than it does of extrafusal muscle. Differential time courses of the action of a drug on intrafusal and extrafusal mammalian muscle are well known from the action of curariform substances on the end-plates of intrafusal and extrafusal muscle (Granit, Homma & Matthews, 1959); transmission at the intrafusal neuromuscular junction is blocked more slowly than that at the extrafusal junction. Once blocked, however, transmission at the intrafusal junction remains blocked for a longer time than that at the extrafusal junction.

However, intrafusal recovery from the effects of dantrolene sodium is more rapid than for extrafusal muscle (Leslie & Part, 1981). This difference would suggest that the differential action of dantrolene sodium on intrafusal and extrafusal muscle cannot predominantly be explained in the manner of curariform drugs in terms of differential access of the drug to the two types of muscle (Matthews, 1972). Furthermore the time course of action of dantrolene sodium on static and dynamic intrafusal muscle is very similar, as opposed to the highly differential action of curariform drugs on these two types (Emonet-Dénand & Houk, 1968); a differential action which has been explained in terms of restricted access of the drug to static gamma fibre nerve endings lying within the spindle capsule (Matthews, 1972).

It seems probable therefore that, whilst differential access is in no way ruled out, intrafusal and extrafusal muscles have absolute differences in their sensitivities to dantrolene sodium. Support is given to this idea by the different final percentage depressions of contraction in intrafusal and extrafusal muscle. It has been proposed that dantrolene sodium acts on the transverse tubule system to reduce the eventual release of calcium from the sarcoplasmic reticulum (Takauji, Takahashi & Nagai, 1975). Intrafusal and extrafusal muscles differ considerably in the density of transverse tubules within the cell. According to Adal (1969) and Banker & Girvin (1971) transverse tubules and sarcoplasmic reticulum are much less conspicuous in intrafusal fibres, both bag and chain, than in extrafusal muscle. Cardiac muscle with its very much less pronounced transverse tubule system, is unaffected by the concentration of dantrolene sodium used in this present work (Ellis *et al.* 1973). It does not seem unreasonable that a muscle with an intermediate complement of transverse tubules and sarcoplasmic reticulum, as has intrafusal muscle, should be affected by dantrolene sodium to an intermediate extent.

We have shown that the depressant action of dantrolene sodium on the spindle afferent response to gamma nerve fibre stimulation is dependent upon the frequency of stimulation. For extrafusal muscle the maximum effect of dantrolene sodium occurs at those frequencies at which the motor units of fast and slow muscle are firing naturally (Bowman *et al.* 1979; Leslie & Part, 1981), and it has been argued that the

reflex motor control systems must operate in some way to adjust the discharge frequencies to higher ones not so profoundly depressed by dantrolene sodium (Leslie & Part, 1981). Nothing is known of firing frequencies of soleus gamma motoneurones in the conscious rat. However in the lightly anaesthetized rat (Andrew, Leslie & Part, 1979) they are at a maximum of about 50 impulses per sec, during pinna pinch. Whilst frequencies in the conscious animal may be higher, it is quite probable that they are ones at which the soleus intrafusal contraction is profoundly depressed by dantrolene sodium. On the other hand, in the lightly anaesthetized rat other muscles such as peroneus have gamma discharge frequencies approximately double that of the soleus (Andrew *et al.* 1979); at these higher frequencies of gamma discharge the effect of the drug, especially under conditions of dynamic stretch, may be negligible.

Dantrolene sodium, as the first directly acting skeletal muscle relaxant, has been advocated as a treatment for spasticity. In its clinical use however it has been shown to be ineffective in certain causes of spasticity while in others it is reasonably successful (Pinder, Brogden, Speight & Avery, 1977). Such variability of effectiveness might seem surprising, considering that dantrolene sodium acts within the muscle fibre rather than on the central motor control (Ellis *et al.* 1973). However, there are a number of other factors in the action of the drug to be taken in account: the frequency-dependent action on extrafusal muscle, the frequency-dependent action on intrafusal muscle, the contrasting action of the drug on the dynamic index of spindle sensory endings under static or dynamic fusimotor control, the feed-back of muscle spindle afferents onto alpha motoneurones and the weak feed-back onto gamma motoneurones (Ellaway & Trott, 1978). In addition the inhibitory action of tendon organs on gamma motoneurones (Ellaway, Murphy & Trott, 1979) must be considered. If all these factors are taken into account it is perhaps rather less surprising that the drug does not act equally effectively on spasticities from a wide variety of causes.

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